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Elevated plasma galectin-3 is associated with near-term rehospitalization in heart failure: A pooled analysis of 3 clinical trials

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Background Rehospitalization is a major cause for heart failure (HF)–related morbidity and is associated with considerable loss of quality of life and costs. The rate of unplanned rehospitalization in patients with HF is unacceptably high; current risk stratification to identify patients at risk for rehospitalization is inadequate. We evaluated whether measurement of galectin-3 would be helpful in identifying patients at such risk.

Methods We analyzed pooled data from patients (n = 902) enrolled in 3 cohorts (COACH, n = 592; PRIDE, n = 181; and UMD H-23258, n = 129) originally admitted because of HF. Mean patient age was between 61.6 and 72.9 years across the cohorts, with a wide range of left ventricular ejection fraction. Galectin-3 levels were measured during index admission. We used fixed and random-effects models, as well as continuous and categorical reclassification statistics to assess the association of baseline galectin-3 levels with risk of postdischarge rehospitalization at different time points and the composite end point all-cause mortality and rehospitalization.

Results Compared with patients with galectin-3 concentrations less than 17.8 ng/mL, those with results exceeding this value were significantly more likely to be rehospitalized for HF at 30, 60, 90, and 120 days after discharge, with odds ratios (ORs) of 2.80 (95% CI 1.41-5.57), 2.61 (95% CI 1.46-4.65), 3.01 (95% CI 1.79-5.05), and 2.79 (95% CI 1.75-4.45), respectively. After adjustment for age, gender, New York Heart Association class, renal function (estimated glomerular filtration rate), left ventricular ejection fraction, and B-type natriuretic peptide, galectin-3 remained an independent predictor of HF rehospitalization. The addition of galectin-3 to risk models significantly reclassified patient risk of postdischarge rehospitalization and fatal event at each time point (continuous net reclassification improvement at 30 days of +42.6% [95% CI +19.9%-65.4%], $P < .001$).

Conclusions Among patients hospitalized for HF, plasma galectin-3 concentration is useful for the prediction of near-term rehospitalization. (Am Heart J 2014;167:853-860.e4.)

Heart failure (HF) affects millions of patients in the United States and Europe[1,2] and is the most common reason for hospitalization and readmission among elderly patients.[3] Despite improvements in outcome with medical and device therapy,[4,5] unplanned readmission rates after HF hospitalization remain high,[6] with enormous economic burden driven by these readmissions; the cost to Medicare of HF-related rehospitalization is estimated to be approximately $8.7 billion in the United States.

Readmission statistics may be considered in 3 phases, with particularly high rehospitalization rates occurring within the first few months after hospital discharge and during the last 2 months before death.[7] The rate of unplanned hospital readmission has been reported to approach 25% within 30 days of initial discharge[8,9] and 30% within 60 to 90 days postdischarge.[10] One-fifth of the patients with acutely decompensated HF who present at the emergency department experience a subsequent HF episode that primarily involves rehospitalization.[11] The high prevalence of unplanned rehospitalizations adversely affects health care costs, resource use, and quality of care and likely will be unsustainable.

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Patient stratification tools that predict risk of near-term readmission would allow clinicians to better focus HF disease management efforts on high-risk patients. Early identification of excess risk using simple blood tests that reflects underlying HF pathophysiology may be useful adjuncts to clinical evaluation in clinical decision making.

Galectin-3 is a β-galactoside–binding lectin with influences in numerous physiologic and pathophysiologic processes in HF.[12] Galectin-3 has shown to be a key mediator of cardiac remodeling[13,14] and organ fibrosis,[15] which are 2 pathophysiologic mechanisms involved in HF disease progression. Although galectin-3 has been identified as a powerful predictor of mortality,[16-18] the usefulness to predict unplanned HF rehospitalization has been less well described.

Given the potential value of galectin-3 testing for predicting near-term clinical outcomes, we studied whether baseline levels of circulating galectin-3 could identify patients with HF at higher risk for near-term rehospitalization. To do so, we studied 3 independent clinical cohorts, together comprising 902 patients with HF, and assessed the value of galectin-3 for prediction of 30-, 60-, 90-, and 120-day rehospitalization and mortality risk.

Methods

Patient populations

We analyzed the rehospitalization rates of hospitalized patients with HF in 3 separate studies, the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH; n = 592), the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE; n = 181), and the University of Maryland Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea study (University of Maryland Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea study [UMD] H-23258; n = 129). The details of each study have been published elsewhere[19-21]; blood samples in each of the 3 cohorts were collected at the time of study enrollment; the other analytes (natriuretic peptides, creatinine) that are presented and used for statistical adjustments were taken simultaneously with the galectin-3 measurement, at the time of enrollment in the respective studies.

In each study, data regarding rehospitalization were available to at least 120 days of follow-up, with complete data available for the total 902 patients. All blood samples in these studies were obtained during the index hospitalization with galectin-3 measured in these index hospitalization blood samples. All studies were reviewed and approved by local institutional review boards, and all patients provided written informed consent.

Biochemical measurements

Plasma galectin-3 levels were determined using a commercially available enzyme-linked immunosorbent assay (BG Medicine, Inc, Waltham, MA). Details are described in the online Appendix Supplementary material.

Outcome measurements

The primary end points were rehospitalization for HF and the composite of rehospitalization for HF and all-cause mortality (first to occur). *Rehospitalization* was defined as an unplanned overnight stay in the hospital due to worsening HF. In each of the studies, patients were characterized by typical symptoms and signs of HF according to the standard criteria. All events in each study were adjudicated by independent clinical event committees.

Statistical methods

Baseline characteristics are presented as means and SDs, or medians and interquartile ranges (IQRs), as indicated, and differences across studies were assessed by analysis of variance modeling for continuous variables and by χ^2 test or Fisher exact test for categorical variables. Fixed-effects Mantel-Haenszel model and the random-effects DerSimonian-Laird model were used to generate summary pooled odds ratios (ORs). Cox proportional hazards regression was used to generate estimates of hazard ratios (HRs) and 95% CIs associated with galectin-3 as a dichotomized variable.

For discrimination and reclassification analyses, the contribution of galectin-3, dichotomized by the cutoff value of 17.8 ng/mL, was assessed. The base model (age, gender, New York Heart Association [NYHA] class, left ventricular ejection fraction [LVEF], estimated glomerular filtration rate [eGFR], and B-type natriuretic peptide [BNP] value [logarithmically transformed]) was compared with a model comprising these same variables plus dichotomized galectin-3. Reclassification was assessed using both the continuous net reclassification improvement (NRI) metric and NRI in which 3 categories were defined by tertiles of predicted risk.[28] Areas under receiver operating characteristic curves (AUROCs) derived from the base model and from the base model plus galectin-3 were compared using the method of deLong et al.[29] which accounts for the correlated nature of the curves.

All statistical analyses were performed at a significance level of .05 (complete statistical elaboration in online Appendix Supplementary material).

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Table I. Baseline characteristics

Characteristics	COACH (n = 592)	PRIDE (n = 181)	UMD H-23258 (n = 129)	*P* value for difference*
Age (y), mean (SD)	70.8 (11.2)	72.9 (13.2)	61.6 (13.4)	<.001
Female, n (%)	227 (38.3)	84 (46.4)	36 (27.9)	.004
Systolic blood pressure (mm Hg)	117.9 (21.0)	139.2 (29.7)	143.8 (26.3)	<.001
Diastolic blood pressure (mm Hg)	68.7 (12.2)	76.6 (17.9)	84.0 (19.0)	<.001
Hypertension, n (%)	256 (43.2)	113 (62.4)	101 (78.3)	<.001
BMI (kg/m^2), mean (SD)	27.1 (5.5)	27.9 (6.3)	31.0 (9.0)	<.001
Diabetes, n (%)	176 (29.7)	72 (39.8)	58 (45.0)	.001
Smoker, n (%)	101 (17.4)	23 (12.7)	40 (31.3)	<.001
HF history				
NYHA				<.001
NYHA I/II, n (%)	275 (46.5)	25 (13.9)	37 (28.7)	
NYHA III, n (%)	293 (49.5)	60 (33.3)	65 (50.4)	
NYHA IV, n (%)	20 (3.8)	95 (52.8)	27 (20.9)	
LVEF (%), mean (SD)	33.3 (14.2)	48.2 (18.3)	37.2 (14.8)	<.001
LVEF >40, n (%)	139 (23.5)	112 (61.9)	39 (30.2)	<.001
Treatment				
ACEi/ARB, n (%)	486 (82.1)	67 (37.0)	62 (48.1)	<.001
β-Blocker, n (%)	398 (67.2)	102 (56.4)	76 (58.9)	.013
Loop diuretic, n (%)	555 (93.8)	103 (56.9)	61 (47.3)	<.001
Digoxin, n (%)	190 (32.1)	42 (23.2)	22 (17.1)	.001
Laboratory measurements				
Galectin-3 (ng/mL), median (IQR)	20.0 (10.6)	14.9 (8.9)	19.8 (12.7)	<.001
Galectin-3 >17.8 ng/mL, n (%)	357 (60.3)	66 (36.5)	79 (61.2)	<.001
eGFR (mL/min per 1.73 m^2), mean (SD)	53.9 (20.2)	56.4 (25.0)	57.0 (24.4)	.20
BNP (pg/mL), median (IQR)	448 (199-908)	386 (174-827)	609 (318-1428)	<.001
NT-proBNP (pg/mL), median (IQR)	2521 (1304-5591)	4299 (1795-9970)	4109 (1532-9577)	<.001

Abbreviations: *BMI*, Body mass index; *ACEi*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker; *n*, number of subjects.
* *P* value for difference of at least 1 study from others.

specimens of this study. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

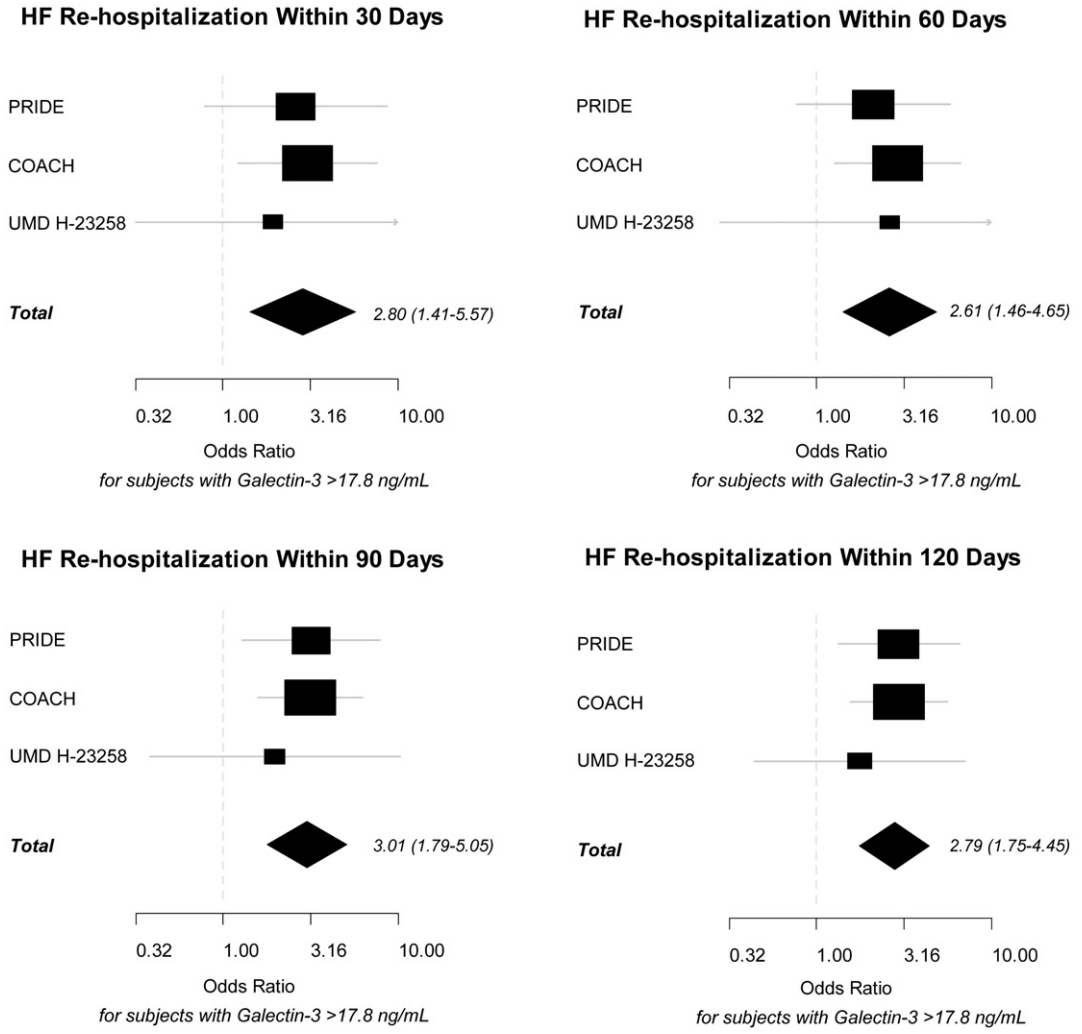
Results

Baseline characteristics of the study patients in each of the 3 studies are presented in Table I. The mean age of patients ranged from 61.6 to 72.9 years, and the proportion of men ranged from 53.6% to 72.1%. Most patients were categorized as NYHA class III and IV, but in the COACH study, which enrolled patients predischarge, approximately half were assessed as NYHA class II. Mean LVEF ranged from 33% to 48%, with a mean (SD) value of 37% (16%) across all studies. In all studies, BNP and N-terminal pro-BNP (NT-proBNP) levels exhibited evident elevation. Online Appendix Supplementary Table I shows the baseline characteristics as a pooled analysis of all patients (n = 902), divided based on the galectin-3 cutoff of 17.8 ng/mL.

Patients with HF having galectin-3 levels greater than 17.8 ng/mL were more likely to be rehospitalized for HF within 30, 60, 90, and 120 days after index discharge in all studies (Figure 1). The pooled ORs were 2.80 (95% CI 1.41-5.57), 2.61 (95% CI 1.46-4.65), 3.01 (95% CI 1.79-5.05), and 2.79 (95% CI 1.75-4.45) for, respectively, 30, 60, 90, and 120 days ($P < .01$ for all time points) (Figure 1 and Table II). The individual ORs were comparable for all studies; because of different number of subjects and events in each constituent study, CIs varied among studies (Figure 1). Analyses for the secondary end point, the composite of all-cause mortality and HF rehospitalization, yielded similar results, with pooled ORs of 1.64 (95% CI 0.97-2.92), 1.99 (95% CI 1.16-3.39), 1.86 (95% CI 1.18-2.94), and 1.84 (95% CI 1.19-2.86), respectively, for 30, 60, 90, and 120 days after discharge for index hospitalization for HF (online Appendix Supplementary Figure 1).

We further evaluated whether galectin-3 levels obtained during the index hospitalization independently predicted subsequent hospital readmission after consideration of established risk factors for HF rehospitalization. For this analysis, we adjusted for age, gender, NYHA class, renal function (eGFR), LVEF, and BNP levels (Table III). We also observed that galectin-3 remained a significant predictor when we considered the composite end point of HF rehospitalization and all-cause mortality (online Appendix Supplementary Table II). Cumulative hazard analyses for the end point of HF rehospitalization, to 120 days after hospitalization discharge, are shown in Figure 2 for each study individually, with index hospitalization galectin-3 value dichotomized as indicated to compare low and high baseline concentrations of galectin-3. Online Appendix Supplementary Table III provides an overview of the exact number of end points (HF rehospitalization and the composite end point), by galectin-3 category and by time.

Figure 1



Odds ratio for HF rehospitalization at different time points. Forrest plot for HF rehospitalization within 30, 60, 90, and 120 days across the 3 studies for patients with galectin-3 >17.8 ng/mL. The size of the cube is proportional to the sample size of each study; the pooled analysis is depicted by a diamond.

Galectin-3 improved reclassification of near-term rehospitalization for HF and mortality when added to the clinical risk model comprising age, gender, NYHA class, eGFR, LVEF, and BNP, at each of the 4 postdischarge time points considered (Table IV). The addition of galectin-3 yielded an NRI ranging from +38.4% to +42.6% in continuous NRI analyses, and +10.7% to +19.3% in analysis in which tertiles of base model risk were used to define 3 risk categories (Table IV) ($P < .05$ for all analyses). Improvement in classification accuracy with galectin-3 was seen in both low-risk and intermediate-risk categories in categorical NRI analyses, at each time point (online Appendix Supplementary Table IV [A-D]). Galectin-3 measurement resulted in correctly increasing the postdischarge risk categorization in 19% to 33% of all patients who were initially inaccurately placed into the lowest-risk category based solely on the clinical risk model, but who subsequently experienced a rehospitalization or death within 30, 60, 90, or 120 days. Finally, the addition of galectin-3 to the base risk model resulted in nonsignificant increases in the AUROC at each time point (Table IV).

Discussion

The main finding of our pooled analysis is that plasma galectin-3 levels independently predict near-term HF rehospitalization and death and yield significantly

Table II. Pooled ORs for galectin-3 >17.8 ng/mL and HF rehospitalization, separately for 30, 60, 90, and 120 days, by fixed-effects and random-effects analysis

	OR (95% CI), fixed effects	*P*	OR (95% CI), random effects	Percentage of patients rehospitalized for HF (across all studies)	
				≤17.8 ng/mL	>17.8 ng/mL
30 d	2.80 (1.41-5.57)	.003	2.78 (1.40-5.52)	3.0	7.3
60 d	2.61 (1.46-4.65)	.001	2.57 (1.44-4.59)	4.5	10.0
90 d	3.01 (1.79-5.05)	<.001	3.01 (1.80-5.04)	5.5	13.6
120 d	2.79 (1.75-4.45)	<.001	2.79 (1.75-4.44)	7.3	15.8

Table III. Cox regression model for HF rehospitalization

Study	Model	HR (95% CI)	χ^2	*P*
COACH	Galectin-3 only (>17.8 ng/mL)	2.35 (1.63-3.39)	21.1	<.001
	Multivariable adjusted*	1.61 (1.04-2.50)	4.47	.034
PRIDE	Galectin-3 only (>17.8 ng/mL)	1.74 (1.11-2.73)	5.8	.016
	Multivariable adjusted*	1.64 (0.99-2.71)	3.65	.056
UMD H-23258	Galectin-3 only (>17.8 ng/mL)	1.82 (0.89-3.90)	2.4	.087
	Multivariable adjusted*	3.15 (1.12-8.88)	4.72	.030

* Adjusted for baseline age, gender, renal function (eGFR), NYHA class, log(BNP), and LVEF.

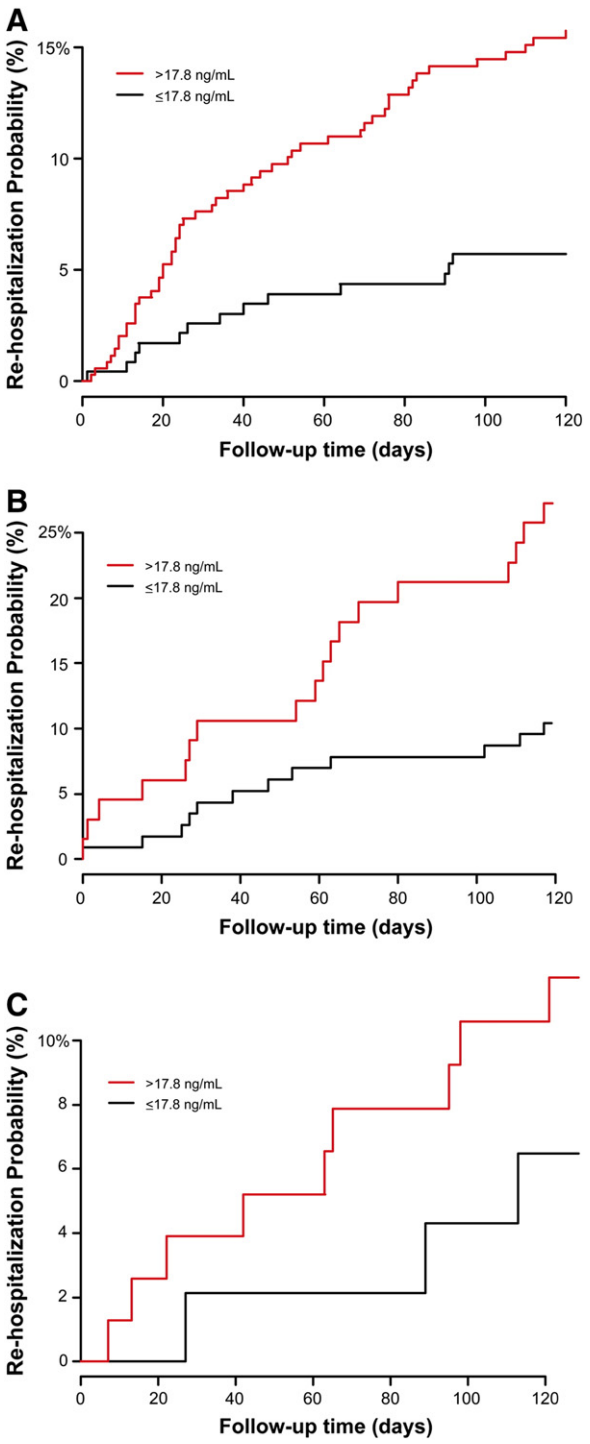
improved risk classification accuracy. Galectin-3 levels exceeding 17.8 ng/mL consistently predicted 30-, 60-, 90-, and 120-day rehospitalization rates in 3 separate HF cohorts, independent of age, gender, kidney function, LVEF, NYHA class, and plasma BNP levels. These results suggest that assessing galectin-3 levels may be useful in the identification of patients with HF at risk for early rehospitalization. Awareness of higher risk for near-term events could potentially be useful in the prevention of unplanned hospitalizations, although the current study did not test clinical decision making guided by galectin-3.

Currently, strong emphasis is put on reducing unplanned rehospitalization after an acute HF admission, the incidence of which may be as high as 25% to 30% within the 30- to 90-day postdischarge period.[8,10,11,27] Hospitals have been pursuing strategies to reduce rehospitalization incidence because of the substantial impact on health care resources and budgets, and associated loss of quality of life and life span in HF. Of note, in the United States, the federal Centers for Medicare and Medicaid Services have recently implemented regulations that impose significant penalties on hospitals with excessive unplanned readmission rates, particularly within the 30-day postdischarge period.[30] Although this benchmark has been strongly debated, hospitals are seeking methods to reduce the rehospitalization rate for HF.[31]

Because reduction of HF rehospitalization is an increasingly urgent objective, physicians and hospitals are seeking more accurate risk stratification tools in patients with HF, with a goal to potentially reduce near-term HF rehospitalization. Currently, several HF risk engines or prediction models have been developed[32,33]; however, to date, there is no established model in use to help individual physicians to classify individual patients with HF at risk for early rehospitalization. The use of circulating biomarkers, particularly ones relevant to aspects of HF pathophysiology, may improve the accuracy of risk stratification as center- and clinician-independent markers of disease severity.

Both BNP and NT-proBNP are routinely used to confirm the diagnosis of HF,[19,34] and several studies have reported their strong prognostic value.[35-38] Data from the Biomarkers in Acute Heart Failure (BACH) trial showed that the predictive performance of BNP, NT-proBNP, and MR-proADM (represented as area under the curve values for 30-day all-cause rehospitalization) is modest at 0.569, 0.501, and 0.510, respectively.[39] Our study shows an additional value of galectin-3 independent of natriuretic peptides. Because changes in cardiac structure and function usually precede symptoms, an ideal strategy for prognosis and risk profiling in HF would not only include markers of mechanical stretch, such as BNP or NT-proBNP, but also markers of inflammation and remodeling. Galectin-3 has been shown a strong predictor of mortality, independent of NT-proBNP levels,[16-18,40] although some studies have suggested that renal function and/or BNP levels attenuate the prognostic power of galectin-3.[41,42] In the present study, galectin-3 was a strong predictor of outcome, even after adjustment for eGFR and BNP levels. Although natriuretic peptides reflect hemodynamic loading and readily respond to

Figure 2



Cumulative hazard analyses for the end point of HF rehospitalization across the 3 studies based on galectin-3. Cumulative hazard analyses for the end point of HF rehospitalization with the baseline galectin-3 value dichotomized to compare low (<17.8 ng/mL) and high (>17.8 ng/mL) concentrations. **A**, COACH: log-rank $P < .001$ **B**, PRIDE: log-rank $P = .006$. **C**, Maryland: log-rank $P = .29$.

ventricular stretch, galectin-3 has been shown to be a marker of active fibrogenesis and ventricular remodeling, and thus less responsive to unloading.[43,44] It may indeed be argued that elevated galectin-3 may signify patients with HF and intrinsic progressive disease that are significantly more prone to unplanned rehospitalization. This is in line with recent observations suggesting that patients with rising concentrations of galectin-3 (observed in approximately 25% of all patients) have an approximately 50% increase in morality and rehospitalization risks.[45] Clearly, rehospitalization is, beside disease-related factors, also influenced by patient-related factors including compliance and access to care. Nevertheless, although the multifactorial nature of rehospitalization makes easy solutions unlikely, biomarkers could provide useful information in predicting which patient is more likely be readmitted. Currently, there are no data suggesting that specific therapies are of additional value when galectin-3 is elevated, so that generic recommendations on clinical therapy in patients with elevated galectin-3 cannot be given.

Strengths and limitations

In our studied cohorts, rehospitalization rates were lower than reported in the literature, possibly because of inclusion bias in clinical trials. Some other limitations inherent to pooled analyses must also be acknowledged, for example, publication bias (for instance, that other studies may have been overlooked) and heterogeneity of results and analyses. The present analysis is a pooled analysis of, as far as we are informed, the 3 largest acute HF cohorts in which galectin-3 was measured and follow-up was available after a hospitalization for HF. An important difference among the 3 studies was that COACH enrolled patients 1 day prior to discharge, whereas the other 2 studies enrolled subjects at the time of admission. Although galectin-3 is known to be a stable marker, galectin-3 levels in COACH patients at the day of hospitalization may have been different. However, galectin-3 predicted near-term rehospitalization, and we demonstrated that increased galectin-3 levels are associated with a nearly 3-fold higher likelihood of subsequent hospitalization. We studied the predictive value in 3 different HF cohorts at 4 time points (30, 60, 90, and 120 months) and analyzed the hospitalization rates and also as a composite end point with all-cause mortality. Our findings across these cohorts were consistent, supporting the possible generalizability of our results.

Conclusion

Upon discharge for hospitalization due to HF, elevated galectin-3 levels are associated with significantly higher risk of near-term readmission for HF, independent of age, gender, renal function (eGFR), NYHA class, LVEF, and natriuretic peptide levels. Galectin-3 testing may be

Table IV. Net reclassification improvement and discrimination change metrics upon the addition of galectin-3, for HF rehospitalization and fatal event, at 30, 60, 90, and 120 days

Time point	NRI, continuous (95% CI)	*P*	NRI, categorical (95% CI)	*P*	Base model, AUROC (95% CI)	Base model + galectin-3, AUROC (95% CI)	*P*
30 d	+42.6% (+19.9%-65.4%)	<.001	+13.3% (+0.3%-26.3%)	.044	0.682 (0.624-0.740)	0.698 (0.644-0.749)	.17
60 d	+39.2% (+19.2%-59.1%)	<.001	+19.3% (+6.8%-31.7%)	.002	0.673 (0.619-0.727)	0.693 (0.642-0.744)	.12
90 d	+40.1% (+22.7%-57.6%)	<.001	+10.8% (+1.2%-20.5%)	.027	0.684 (0.642-0.736)	0.703 (0.657-0.749)	.15
120 d	+38.4% (+21.9%-54.9%)	<.001	+10.7% (+2.1%-19.3%)	.015	0.689 (0.642-0.735)	0.700 (0.654-0.744)	.27

Base model comprises age, gender, NYHA class, LVEF, eGFR, and $\log_e$(BNP) value. Continuous NRI and categorical NRI are for base model plus galectin-3 (dichotomized variable, defined by the cutoff value of 17.8 ng/mL). Categories for categorical NRI are defined by tertiles of predicted risk at each time point.

considered, likely in combination with other risk factors, in programs aiming to reduce hospital readmission rates for HF.

Disclosures

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Appendix A. Supplementary data

BG medicine galectin-3 enzyme-linked immunosorbent assay

The assay quantitatively measures the concentration of human galectin-3 levels, with a limit of detection of 1.13 ng/mL and no reported cross-reactivity with collagen analytes or other members of the galectin family. Calibration of the assay was performed according to the assay instructions for use. Concentration values were assigned using a standard curve[22] evaluated in various HF cohorts[23,24] and the general population.[25] To assign patients to relative risk categories based on galectin-3 value, a threshold value of 17.8 ng/mL was applied, in accordance with the US Food and Drug Administration–cleared assay labeling for risk stratification for this galectin-3 assay. The same assay was used in all 3 analyzed studies, and the analytical performance and coefficient of variability of the assay have been published in detail elsewhere.[22]

Statistical methods

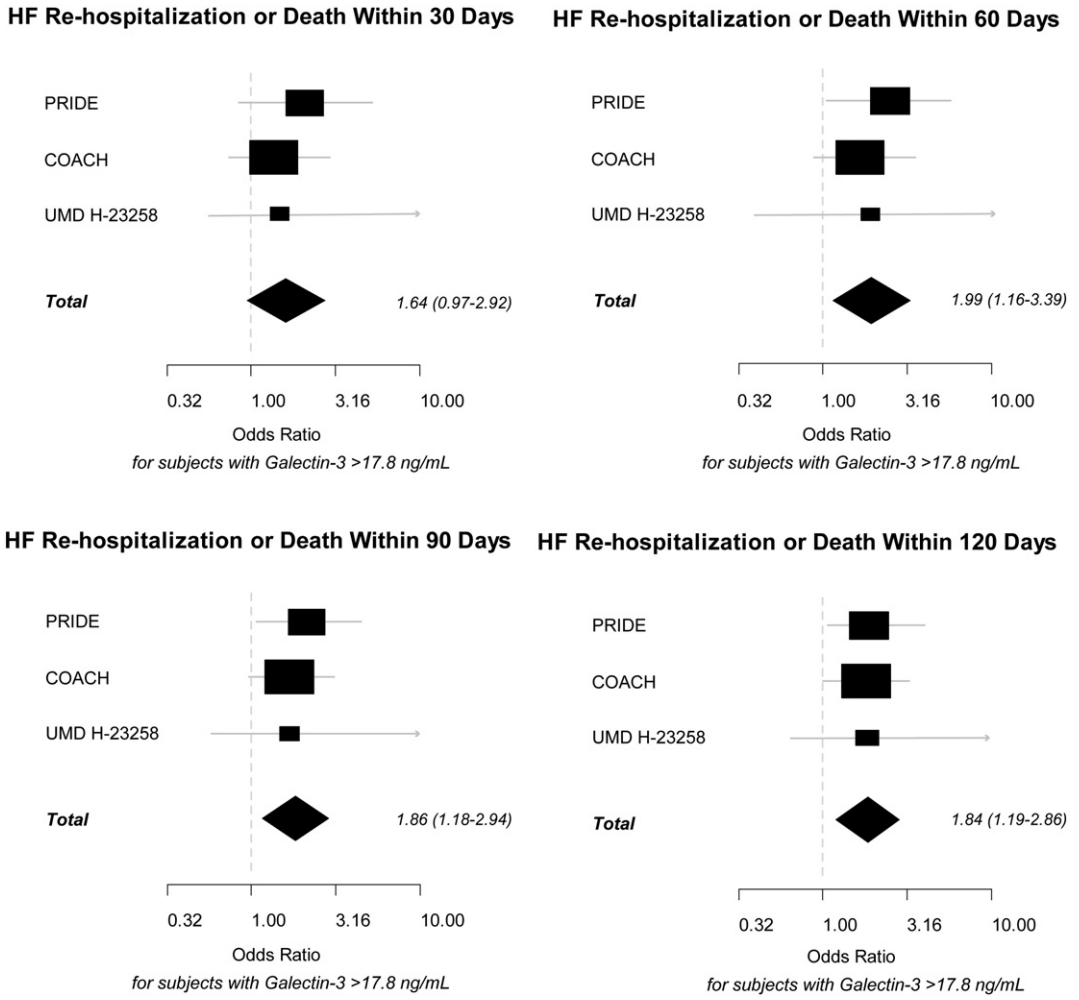
Baseline characteristics are presented as means and SDs, or medians and IQR, as indicated, and differences across studies were assessed by analysis of variance modeling for continuous variables and by χ^2 test or Fisher exact test for categorical variables. To pool results across studies, the fixed-effects Mantel-Haenszel model and the random-effects DerSimonian-Laird model were used to generate summary pooled ORs for each end point at the prespecified time points of 30, 60, 90, and 120 days. Univariate models comprising solely galectin-3, dichotomized by the cutoff value of 17.8 ng/mL, were evaluated. In separate analyses using Mantel-Haenszel and DerSimonian-Laird models, summary ORs were generated that were adjusted for the baseline covariates of age, gender, NYHA class, LVEF, eGFR (calculated using the Modification of Diet in Renal Disease methodology), and baseline BNP value. Prior studies have reported a broad spectrum of predictors of adverse outcomes in HF, and in our analyses, we adjusted for those predictors most closely associated to HF rehospitalization in order to keep statistical models parsimonious.[26,27]

Cumulative incidence functions were generated according to baseline galectin-3 category. For each study separately, Cox proportional hazards regression was used to generate estimates of HRs and 95% CIs associated with galectin-3 as a dichotomized variable and the indicated end point. In Cox regression analyses, Martingale residuals were inspected for satisfaction of the linearity assumption of the Cox regression models.

For discrimination and reclassification analyses, the contribution of galectin-3, dichotomized by the cutoff value of 17.8 ng/mL, was assessed for the prespecified times of 30, 60, 90, and 120 days after index discharge. In these analyses, the base model comprising age, gender, NYHA class, LVEF, eGFR, and BNP value (logarithmically transformed) was compared with a model comprising these same variables plus dichotomized galectin-3, and data from all 3 studies were merged. Reclassification was assessed using both the continuous NRI metric, which is a version of NRI that does not require a priori–defined categories, and NRI in which 3 categories were defined by tertiles of predicted risk.[28] All subjects complete on all variables in the base model and on galectin-3, and with complete follow-up to the specified time point, were included in reclassification calculations. Areas under receiver operating characteristic curves derived from the base model and from the base model plus galectin-3 were compared using the method of deLong et al,[29] which accounts for the correlated nature of the curves.

All statistical analyses were performed at a significance level of .05. Analyses were performed with SAS software, version 9.1 (SAS Institute, Inc, Cary, NC), or R software, version 3.1 (R Foundation for Statistical Computing, Vienna, Austria). Reclassification calculations were performed using the R package "PredictABEL," version 1.2-1 (Erasmus Medical Center, Rotterdam, the Netherlands).

Supplementary Figure 1



Odds ratio for HF rehospitalization or death at different time points. Forest plot for HF rehospitalization or all-cause mortality within 30, 60, 90, and 120 days across the 3 studies for patients with galectin-3 > 17.8 ng/mL. The size of the cube is proportional to the sample size of each study; the pooled analysis is depicted by a diamond.

Supplementary Table I. Baseline characteristics by galectin-3 category

Characteristic	Galectin-3 ≤ 17.8 ng/mL (n = 400)	Galectin-3 > 17.8 ng/mL (n = 502)	P
Age (y), mean (SD)	67.8 (12.7)	71.8 (11.8)	<.001
Female, n (%)	133 (33.3)	214 (42.6)	.004
Systolic blood pressure (mm Hg)	126.4 (25.6)	125.5 (26.7)	.61
Diastolic blood pressure (mm Hg)	73.0 (15.6)	72.0 (15.7)	.36
Hypertension, n (%)	194 (48.5)	276 (55.0)	.11
BMI (kg/m^2), mean (SD)	28.1 (6.5)	27.7 (6.3)	.39
Diabetes, n (%)	106 (26.5)	200 (39.8)	<.001
Smoker, n (%)	74 (18.5)	90 (17.9)	.40
HF history			
NYHA			.011
NYHA I/II, n (%)	169 (42.5)	168 (33.7)	
NYHA III, n (%)	164 (41.2)	254 (50.9)	
NYHA IV, n (%)	65 (16.3)	77 (15.4)	
LVEF, mean (SD)	38.5 (17.2)	35.5 (15.6)	.010
LVEF >40, n (%)	149 (37.3)	141 (28.1)	.003
Treatment			
ACEi/ARB, n (%)	263 (65.8)	352 (70.1)	.36
β-Blocker, n (%)	256 (64.0)	320 (63.7)	.60
Loop diuretic, n (%)	292 (73.0)	427 (85.1)	.002
Digoxin, n (%)	107 (26.8)	147 (29.3)	.54
Laboratory measurements			
eGFR, mL/min per 1.73 m^2, mean (SD)	65.5 (19.9)	46.4 (19.6)	<.001
BNP (pg/mL), median (IQR)	389 (174-771)	511 (243-1250)	<.001
NT-proBNP (pg/mL), median (IQR)	2238 (1164-4706)	3727 (1701-9803)	<.001
Galectin-3 (ng/mL), median (IQR)	13.7 (4.6)	24.5 (10.2)	<.001

Abbreviations: *BMI*, Body mass index; *ACEi*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker.

Supplementary Table II. Cox regression model for the composite end point (HF rehospitalization and all-cause mortality)

Study	Model	HR (95% CI)	χ^2	P
COACH	Galectin-3 only (>17.8 ng/mL)	2.18 (1.65-2.89)	29.5	<.001
	Multivariable adjusted*	1.46 (1.02-2.08)	4.33	.037
PRIDE	Galectin-3 only (>17.8 ng/mL)	1.48 (1.06-2.07)	5.1	.023
	Multivariable adjusted*	1.41 (0.97-2.06)	3.09	.077
UMD H-23258	Galectin-3 only (>17.8 ng/mL)	1.85 (1.01-3.38)	3.9	.049
	Multivariable adjusted*	2.41 (1.10-5.28)	4.82	.031

*Adjusted for baseline age, gender, renal function (eGFR), NYHA class, log(BNP), and LVEF.

Supplementary Table III. Counts of HF rehospitalization and composite end point (HF rehospitalization and all-cause mortality) across all studies, by galectin-3 category and by time

		Galectin-3 ≤ 17.8 ng/mL	Galectin-3 > 17.8 ng/mL
30 d	HF rehospitalization, n (%)	11 (2.8)	39 (7.8)
	Composite end point, n (%)	20 (5.0)	63 (12.6)
60 d	HF rehospitalization, n (%)	16 (4.0)	53 (10.6)
	Composite end point, n (%)	31 (7.8)	87 (17.3)
90 d	HF rehospitalization, n (%)	21 (5.3)	72 (14.3)
	Composite end point, n (%)	42 (10.5)	117 (23.3)
120 d	HF rehospitalization, n (%)	28 (7.0)	83 (16.5)
	Composite end point, n (%)	53 (13.3)	136 (27.1)

Supplementary Table IV. (A-D) Reclassification tables indicating counts of patients in each risk category, by time point and by patient fate, based on the addition of galectin-3 to the base risk model without galectin-3

Model without galectin-3		**Model with galectin-3**		
A. *T* = 30 d				
Patients with events	<5.9%	5.9%-9.4%	>9.4%	% Reclassified
<5.9%	6	2	0	25%
5.9%-9.4%	2	10	10	55%
>9.4%	0	4	32	11%
Patients without events				
<5.9%	221	37	0	14%
5.9%-9.4%	72	109	45	52%
>9.4%	0	40	184	18%
B. *T* = 60 d				
Patients with events	<8.5%	8.5-13.3%	>13.3%	% Reclassified
<8.5%	8	4	0	33%
8.5%-13.3%	5	12	19	67%
>13.3%	0	5	40	11%
Patients without events				
<8.5%	208	36	0	15%
8.5%-13.3%	75	97	49	56%
>13.3%	0	46	170	21%
C. *T* = 90 d				
Patients with events	<11.8%	11.8-19.0%	>19.0%	% Reclassified
<11.8%	13	3	0	19%
11.8%-19.0%	7	23	17	51%
>19.0%	0	7	60	10%
Patients without events				
<11.8%	206	35	0	15%
11.8%-19.0%	64	111	33	47%
>19.0%	0	44	150	23%
D. *T* = 120 d				
Patients with events	<12.1%	12.1-22.0%	>22.0%	% Reclassified
<12.1%	6	3	0	33%
12.1%-22.0%	4	33	21	43%
>22.0%	0	10	78	11%
Patients without events				
<12.1%	87	15	0	15%
12.1%-22.0%	50	233	44	29%
>22.0%	0	35	154	19%

At each time point, patients who are complete on all variables included in the base model and on galectin-3, and with complete follow-up to the specified time point, are evaluable in reclassification calculations. The base risk model comprises age, gender, NYHA class, LVEF, eGFR, and BNP value.